

# Dynamic patterns of avian and human influenza in east and southeast Asia

Andrew W Park, Kathryn Glass

The seasonal patterns of human influenza in temperate regions have been well documented; however, much less attention has been paid to patterns of infection in the tropical and subtropical areas of east and southeast Asia. During the period 1997–2006, this region experienced several outbreaks of highly pathogenic avian influenza A (H5N1) in hosts including wild and domestic poultry, human beings, and other mammals. H5N1 is thought to be a likely source of a pandemic strain of human influenza. Incidence of both human influenza and avian influenza in human beings shows evidence of seasonality throughout east and southeast Asia, although the seasonal patterns in tropical and subtropical areas are not as simple or as pronounced as those in temperate regions around the world. The possibility of a human being becoming co-infected with both human and avian strains of influenza is not restricted to a short season, although the risks do appear to be greatest during the winter months.

## Introduction

In Hong Kong in 1997, an outbreak of highly pathogenic avian influenza A (H5N1) spread from poultry to human beings, causing 18 confirmed cases and six deaths.<sup>1</sup> Between 2001 and 2006, outbreaks of H5N1 occurred in poultry every year in various parts of east and southeast Asia and led to around 200 confirmed human cases in the region.<sup>2</sup> As yet, the virus has shown very limited ability to spread from person to person. However, if a strain of influenza that is highly pathogenic to human beings acquires the ability to spread easily between human beings, the result could be a global pandemic such as that seen in 1918–19, which killed an estimated 40 million people.<sup>3,4</sup>

A pandemic strain could arise either by adaptive mutation of a zoonotic influenza A virus during human infection, or by genetic reassortment of a zoonotic virus with a human virus in a person simultaneously infected with both human and avian strains of influenza A. Although H5N1 has now spread more widely, much of the recent activity remains in the region of east and southeast Asia, which is considered to be a “hot spot” for the emergence of pandemic influenza because of the close contact between human beings and poultry in live bird markets and farms.

In many regions around the world, there is a wealth of data on influenza incidence in human beings. These regions tend to be temperate and show a strong seasonality characterised by a single peak in the winter months lasting between 8 and 12 weeks. By contrast, there has been relatively little work looking at the temporal patterns of human influenza A in east and southeast Asia, which contains both tropical and subtropical areas. Although there is some evidence that survival of the H5N1 avian influenza virus is temperature dependent,<sup>5</sup> there has been limited investigation into the seasonal patterns of incidence. Moreover, there is a pressing need to monitor these data for evidence of changes in the patterns of incidence and for evidence of expanding host range.

In this paper, we present a review of the data on human and avian influenza H5N1 in east and southeast Asia between 1997 and 2006. Not only do these data give valuable insights into the risk of the emergence of a pandemic strain

of influenza, they also show dynamic trends, revealing which patterns are robust and which are changing. Armed with this information, we are able to monitor important changes in avian influenza epidemiology expressed at the population level, aiding strategic planning in surveillance, control, and pandemic preparedness.

## Search strategy and selection criteria

To investigate the seasonality of H5N1 virus, outbreaks of H5N1 involving morbidity and mortality of domestic poultry were identified using data from the World Organisation for Animal Health for outbreaks from late 2003 onwards,<sup>6</sup> and published articles on outbreaks in Hong Kong between 1997 and 2003.<sup>1,7,8</sup> In some cases, isolates from poultry markets indicated that H5N1 virus was present before mortality was observed;<sup>1,7</sup> however, because surveillance was not uniform across time and all locations, we included identified outbreaks only. For each region and year in which an outbreak occurred, we classified each month according to the number of outbreaks in that month: none, 1–9 outbreaks, 10–99 outbreaks, and 100 or more outbreaks. Where the data-reporting period included more than 1 month, outbreaks were split between months according to the number of days in the reporting period in that month.

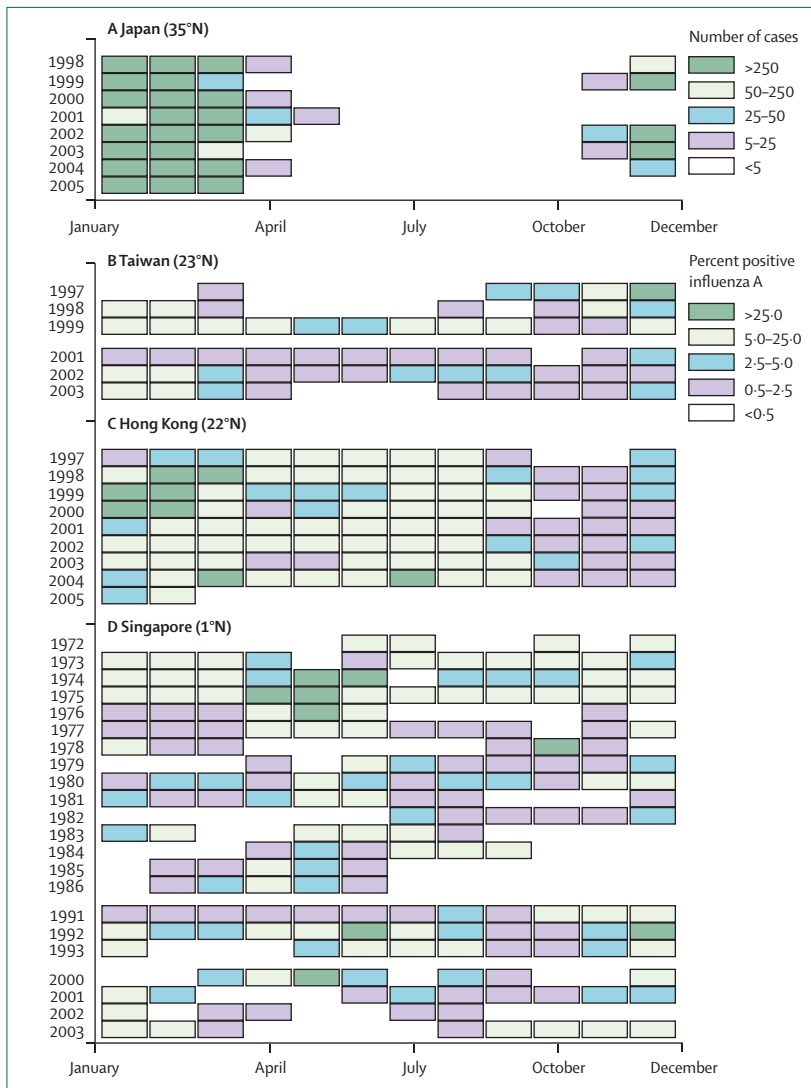
Data on human cases of H5N1 virus from late 2003 onwards were obtained from WHO,<sup>2</sup> with data on human cases in Hong Kong between 1997 and 2003 taken from published articles.<sup>9,10</sup> The reference date for each case was taken to be the date of onset of symptoms, if available, otherwise the date of hospitalisation was used. For each region, the presence or absence of (at least) one human H5N1 case was recorded for each 10-day period.

A search using PubMed (using the search terms “avian influenza”, “H5N1”, and “surveillance”) for English language articles with surveillance data extending over at least 1 year identified only one article that included H5N1 isolates. These data were collected from live poultry markets in mainland China from July, 2000, until January, 2004.<sup>11</sup> Since there is evidence that ducks and geese in central China had an important role in the persistence and

*Lancet Infect Dis* 2007; 7: 543–48

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**Figure 1: Seasonality of human influenza A cases in east and southeast Asia**  
The data from (A) Japan<sup>14</sup> show monthly cases of influenza A, whereas data from (B) Taiwan,<sup>15,16</sup> (C) Hong Kong,<sup>17</sup> and (D) Singapore<sup>18-20</sup> show percentage of isolates positive for influenza A.

reassortment of the virus over this period,<sup>12,13</sup> we include these data for comparison.

To investigate the seasonality of human influenza A, we searched the published scientific literature using Web of Science and PubMed for studies that reported confirmed instances of human influenza A viruses in populations in east and southeast Asia over the years 1996–2005. These data are presented in figure 1, using colour scales that capture even small levels of influenza A activity, with less focus on distinguishing between high activity months. The data for Japan give the number of reported, confirmed cases by month (1998–2005)<sup>14</sup> and the data for Taiwan (1997–99 and 2001–03),<sup>15,16</sup> Hong Kong (1997–2005),<sup>17</sup> and Singapore (2000–03)<sup>18</sup> give the percentage of isolates that tested positive for influenza A. Since there were limited years of data for Singapore over this period, we have also

included earlier data from 1972–86 and 1991–93.<sup>19,20</sup> Two independent studies from Hong Kong—one using reported, confirmed cases<sup>21</sup> and the other using the percentage of influenza positive isolates<sup>22</sup>—gave very good agreement on influenza activity in the years in which the studies overlapped (1998–99). The data for Taiwan for 1997–99 are age-biased (only children aged 12 years and under were sampled). To compare influenza data from east and southeast Asia with that from outside the region, data giving the percentage of influenza positive isolates in the USA over the period 1998–2004 were obtained from the US Centers for Disease Control and Prevention.<sup>23</sup>

To establish changes in patterns of host range and seasonality, a literature search was done covering the period from 1996 to 2006 (using Web of Science, WHO, World Organisation for Animal Health, PubMed, Scirus) to establish when H5N1 virus isolation from various host species was confirmed. The links between the dynamic host range and sporadic appearance of H5N1 in human beings and chickens was investigated.

### Seasonality of H5N1 virus

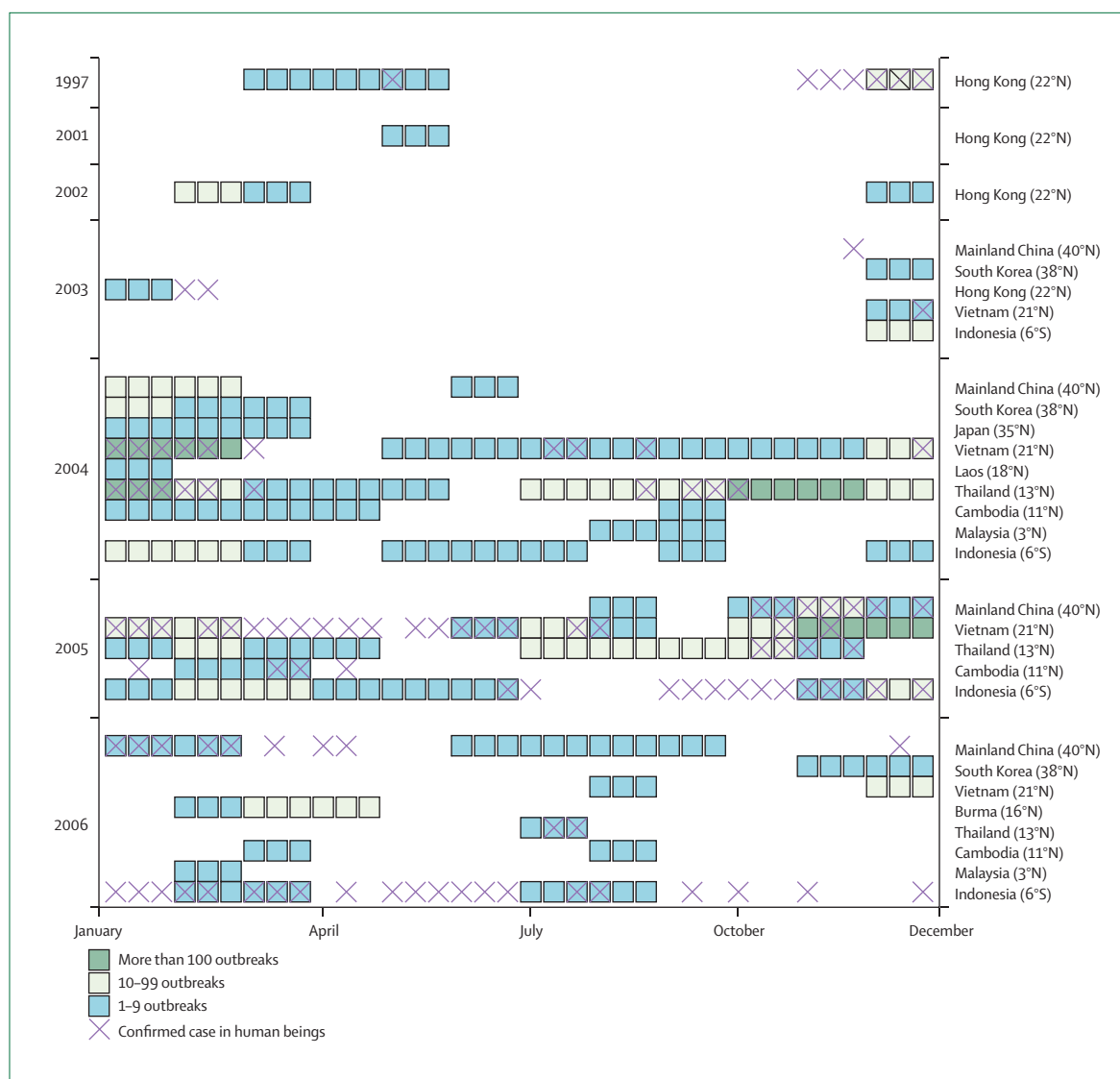
The risk of a pandemic strain of influenza emerging from the circulating H5N1 virus is strongly influenced by the timing and extent of outbreaks of disease. Although wild aquatic birds may have a more important role in persistence of the virus strain, most confirmed cases of H5N1 in human beings report recent contact with domestic poultry. We collated data on cases of H5N1 influenza in human beings and H5N1 outbreaks in domestic poultry over the period 1997–2006, to identify seasonality of H5N1 influenza virus, and to investigate any changes in the seasonal patterns over this period.

Figure 2 shows the seasonality in outbreaks of avian influenza in poultry and confirmed human cases across east and southeast Asia between 1997 and 2006. Human cases largely coincide with those in poultry, although on some occasions they occur before or shortly after the main poultry outbreaks. Figure 3 shows the percentage of isolates positive for H5N1 by month from samples taken from aquatic and terrestrial poultry in mainland China during the period July, 2000 to January, 2004.<sup>11</sup> The data show a strong seasonal pattern of H5N1 infection, with a greater percentage of birds positive for the virus during the winter months.

The seasonal pattern detected in H5N1 surveillance data of isolates taken from live poultry markets in China is broadly similar to the seasonality in poultry outbreaks over this period, with the majority of outbreaks commencing during winter. However, a number of outbreaks extended into (or were reignited in) the summer months, indicating that the risks are not confined to winter.

### Seasonality of human influenza A

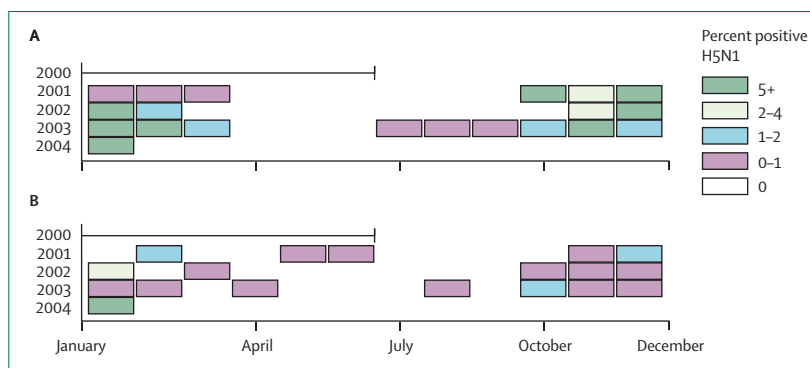
One of the mechanisms for the emergence of a pandemic strain of influenza is co-infection of a human host with an avian strain and a human strain, subsequent genetic



**Figure 2: Seasonality of avian influenza A virus (H5N1) outbreaks in poultry and cases in human beings 1997–2006**

The number of outbreaks in poultry is classified by month as low (blue), medium–high (pale green), and very high (dark green). A cross indicates the presence of confirmed human cases in any 10-day period. The right vertical axis shows the latitude of the capital city of each country included.

reassortment and the genesis of a virus with the highly pathogenic nature of some avian strains seen in human beings, combined with the highly transmissible nature of human influenza. This mechanism requires avian and human strains to be circulating at the same time. Most of the data concerning seasonal appearance of influenza A in human beings comes from temperate regions (eg, Europe, North America, Australia), although there is some evidence of higher levels of respiratory viral infections during the rainy seasons in the tropics.<sup>24</sup> Influenza surveillance data from the Pacific basin collected from 1954 to 1988 indicates that there is marked variation of influenza A activity in human beings in this region.<sup>25</sup> We collated patterns of human influenza A in four locations across east and southeast Asia from the

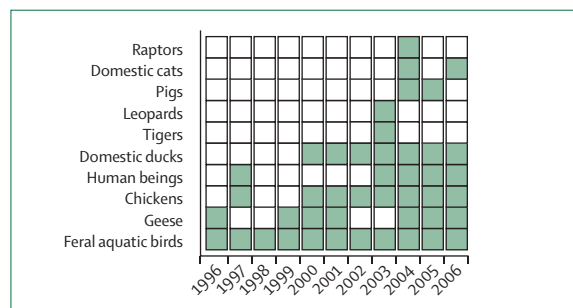


**Figure 3: Percentage of isolates positive for avian influenza A (H5N1) per month from samples taken from poultry markets in mainland China from July, 2000 to January, 2005**  
Monthly percentage positive in (A) aquatic and (B) terrestrial birds. Data from Li et al (2004).<sup>11</sup>

time when avian influenza A (H5N1) was confirmed to have spread to human beings.

Japan showed a strong, consistent seasonality of influenza A activity between December and March. Elsewhere, the seasonality varied between regions and between years in the same region. Taiwan exhibited moderate to high activity in January to February, July to August, and November to December. The 9 years of data for Hong Kong showed influenza A activity was low in October to December but could be moderate to high at all other times. Singapore had moderate to high influenza A activity in most months of the year. A comparison of the percentage of human influenza A positive isolates from the USA and Hong Kong between 1998 and 2004 showed that in Hong Kong there were substantially more months when 10% of samples or more tested positive (41 of 84 months in Hong Kong, compared with 16 of 84 months in the USA). A substantial difference was seen even when this threshold was raised to 20% or more positive isolates, since 15 of the 84 months in Hong Kong qualified compared with only 7 of 84 months in the USA. The USA shows one seasonal peak per year (in winter), during which the mean number of consecutive months with at least 10% of positive samples was 2–3 months. In the same 7 years in Hong Kong, there were ten periods during which at least 10% of samples tested positive and the mean duration of such a period was 4–1 months. Although the influenza burden, measured by hospitalisation and mortality rates, is similar in tropical and temperate regions,<sup>21,22,26,27</sup> the duration of influenza in the two populations is not.

Seasonal patterns in influenza A activity in human populations in east and southeast Asia certainly exist, but these patterns are not uniform across the region. Periods of moderate to high activity typically last longer in tropical and subtropical regions than in temperate regions, and they occur more frequently than once a year. It is not prudent to assume there is a short period of risk of reassortment. As outlined by Simmerman and colleagues<sup>28</sup> (whose data is not included here because the investigators did not distinguish between influenza A and B), and by Viboud and colleagues,<sup>27</sup> more surveillance of influenza A in human beings in parts of east and southeast Asia would be very useful, especially where H5N1 has been detected.



**Figure 4:** The reported host range of avian influenza A viruses (H5N1) 1996–2005

Colour represents that H5N1 is present in the host species.

## Changes in patterns of host range and seasonality

The number of different host species for H5N1 viruses affects the risk of emergence of a pandemic strain in the human population, because there is a chance of viral mutation during each replication cycle of the virus in each host. Therefore, at the population level, mutations arise at a higher rate if more hosts are infected. Similarly, if the virus acquires new host species then this will further increase the overall potential for mutation of the virus. Analysis of the dynamic changes in the host range of the virus helps to differentiate between sporadic appearances in a species and more frequent (potentially endemic) representation. New host populations in which the virus is endemic represent new risks of pandemic influenza in human beings, especially if there is close contact between people and the endemically infected species. Such species increase the risk of reassortment because the avian strain will be present all year round and can coincide with any human influenza season.

All haemagglutinin subtypes are endemic in feral aquatic birds.<sup>29</sup> The proposed donor gene for the haemagglutinin of the 1997 highly pathogenic avian influenza in Hong Kong (which caused human mortality) was isolated from geese in 1996.<sup>30</sup> Between 1999 and 2001, H5N1 viruses were isolated from geese, chickens, and domestic ducks, and they have subsequently been isolated from domestic ducks in every year to 2005. Experimental infection studies show that viruses isolated from ducks between 2000 and 2002 became progressively more pathogenic to mice.<sup>12</sup> Moreover, the duration of viral shedding by ducks increased between 2003 and 2004, although the animals often did not display symptoms of illness.<sup>31</sup> The same laboratory report also indicated that the virus became more environmentally stable over the period 1997–2004, with viruses from 2004 surviving at 37°C for 6 days, compared with 2 days for viruses from 1997.<sup>31</sup> Between 2003 and 2005, the virus acquired several new host species (tigers, leopards, pigs, raptors, and domestic cats; see figure 4).<sup>32–36</sup>

During the past 10 years, the reported host range of H5N1 viruses has increased. Perhaps of greatest concern is both the regularity with which H5N1 is found in domestic ducks (in view of the close contact between these animals and human beings) and the isolation of H5N1 from pigs in China and Indonesia. Pigs have both avian and human influenza sialic acid residue receptors on their respiratory tract,<sup>37</sup> and so could be candidates for generating reassortant strains (which requires co-infection with human and avian strains).

## Discussion

Despite the availability of many high quality data sets, the strong seasonal patterns seen in human influenza incidence in temperate regions are not fully understood. Influenza incidence peaks in the UK and Australia during the winter months, with a 6-month phase difference

between the two locations.<sup>38</sup> This suggests that transmissibility is environmentally dependent. However, it is also plausible that the seasonality could be augmented (or possibly driven) by adult commuters<sup>39</sup> or by the school terms, during which time the contact rate between children increases.<sup>40</sup> Dynamic resonance has also been put forward as an explanation of how even small, almost imperceptible, changes in the transmission rate can be amplified to generate seasonality in disease incidence.<sup>40</sup> Human influenza in tropical and subtropical regions shows more diverse behaviour. Of the human influenza data we collated in east and southeast Asia, only Japan displayed a consistent seasonal pattern in human influenza activity. Other locations (Taiwan, Hong Kong, and Singapore) had medium to high influenza activity over a range of months covering almost all seasons. The extent to which influenza activity depends on factors such as temperature, humidity, and population density remains uncertain, and is confounded by the possibility of under-reporting and misdiagnosis. However, it is clear that the temperate climate model of human influenza incidence does not apply in much of east and southeast Asia.

Highly pathogenic influenza A (H5N1) has appeared in poultry populations in east and southeast Asia since 1997, with human cases closely coupled to the sympatric appearance of H5N1 virus in poultry. Generally, activity has been confined to the months of December to March with only low activity at other times of the year, and there is some evidence that survival of the virus is influenced by temperature.<sup>5</sup> However, these outbreak patterns are strongly influenced by intervention—around 1.5 million chickens were culled in the last few months of 1997 in Hong Kong,<sup>1</sup> and another million were culled in early 2002,<sup>7</sup> interrupting transmission in both cases. It is unclear whether the same patterns would have occurred if the disease was less stringently controlled. More recently, medium to high H5N1 influenza activity has been observed in Thailand during July to November. If the appearance of H5N1 virus in poultry populations was seasonal during 1997–2003 then it appears less constrained in 2004–2006 (figure 2). Li and colleagues<sup>11</sup> suggest that H5N1 viruses with pandemic potential have become endemic in the region and will not be eradicated easily.

Nonetheless, the seasonal appearance of avian influenza in poultry needs to be explored because this might help to elucidate the mechanism for emergence of highly pathogenic strains of avian influenza in human beings. Migratory waterfowl have been implicated as a possible source for the frequent appearance of avian influenza in poultry during the months of December to March. Collectively, feral aquatic birds carry all subtypes of influenza, usually with no signs of illness,<sup>29</sup> and these birds migrate south at the beginning of winter. However, they usually arrive at their wintering grounds by late November or early December.<sup>41</sup> The timing of the migration, combined with the geographic distribution of H5N1 in poultry—which does not resemble any known migration route—has

raised doubts about the importance of migratory birds in the spread of the virus.<sup>41</sup> Movement of infected animals and meat has also been suggested as an explanation for the sporadic appearance of H5N1,<sup>41,42</sup> although this seems an incomplete explanation of the temporal appearance of the virus, which until recently has been concentrated in the months of December to March (figure 2).

Seasonality in both human and avian influenza might influence the season of emergence of a pandemic strain of influenza, although the latter virus is most relevant if a pandemic strain arises through adaptive mutation of an avian virus in the human host. If we examine evidence from past pandemics, we find some uncertainty as to the origin of the 1918 pandemic;<sup>37</sup> however, the 1957 pandemic emerged in China in February, and the 1968 pandemic emerged in mainland China and was detected in Hong Kong in July.<sup>43</sup> Most historical evidence before the 20th century comes from sources in western Europe, and generally indicates Russia as the source of several European outbreaks,<sup>3</sup> with the first cases identified between November and January.<sup>3,4</sup> Earlier references can be found to outbreaks in China and southeast Asia, with the first mention of cases occurring in autumn and winter.<sup>3,4</sup> The pattern of spread of the virus suggests that migratory birds might be involved, whereas the timing of the outbreaks suggests that the risk of pandemic emergence is greatest during the autumn and winter months.

As part of pandemic planning, it is important to quantify the risk of viral reassortment under plausible assumptions concerning rates of infection.<sup>44</sup> However, it is also important that these calculations take account of seasonality in infection rates in areas at high risk for pandemic emergence. The data on human and avian influenza outbreaks indicate that it is not prudent to assume that there is a short period of risk of reassortment every year. Moreover, the relative timing of human and avian influenza incidence is a key factor when assessing these risks. If a peak in human influenza coincides with a peak in human cases of avian influenza, the risk of co-infection and reassortment increases considerably.

Looking to the future, the suggestion that H5N1 virus has become endemic in ducks<sup>11</sup> is of great concern. Previous poultry culls have been successful at containing the spread of avian influenza,<sup>41</sup> but if the virus is endemic in certain species then this is not a practical control measure. It might be necessary to turn attention to vaccination<sup>45,46</sup> and intense surveillance. However, the recent re-emergence of avian influenza in poultry in Vietnam, despite mass culling and vaccination, is a stark reminder of the global challenge posed by the virus. When faced with the prospect of human exposure to this avian influenza strain over a prolonged period of time, awareness of seasonality in the risk of both human disease and viral reassortment can inform control measures to help reduce the possibility of pandemic emergence.



### Search strategy and selection criteria

These are described in detail on page 543.

### Conflicts of interest

We declare that we have no conflicts of interest.

### Acknowledgments

AWP acknowledges Mathematics of Information Technology and Complex Systems (MITACS) funding and a visiting fellowship from the Australian National University. KG acknowledges financial support from the Australian National Health and Medical Research Council (NHMRC) grant 224215.

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